Statistical Review and Evaluation

Date: AUG - 4 1995

PLA #: 94-0308

Applicant: Thomae/Boehringer Ingelheim (BI) GmbH

Name of Product: [redacted] -- the NR-LU-10 Imaging Agent

Document Reviewed: Sponsor's Response dated April 27, 1995 to FDA Questions of Dec 27, 1994

The sponsor submitted responses to FDA questions. The sponsor has provided adequate justification that there is no statistically significant differences in the imaging performance characteristics (sensitivity, PPV, etc.) between the Consensus interpretations versus blinded Interpretation of the scans. The interpretations were classified as follows:

R1 -- the First Reviewer or the primary investigator who had knowledge of prior diagnostic tests, technical information concerning the imaging procedure, and clinical data about the patient.

R2 -- Second Reviewer who read all the scans without any of the diagnostic, clinical or technical information available to the first reviewer.

Rev2-- A formal analysis of staging and detection results based on the readings of the second reviewers alone *corrected for technical artifact*. This analysis was not done previously.

R3 -- Resolved discrepancies of the first and second reviewer who knew nothing about the patient except that a discrepancy existed in the readings between the Primary Investigator and Second Reviewer.

Cons. -- Consensus Interpretation

The sponsor supplied additional data for the Rev2. These data are summarized Tables 1 through 4.

TABLE 1 **Estimates of Imaging Performance Parameters for the Eligible Study Patients with Limited or Extensive Disease as Defined by NR-LU-10 Imaging or the Standard Battery of Tests Assuming that the Standard is Correct, i.e., the discrepancies are resolved in favor of Standard Tests**

TRUE STAGE		NR-LU-10--Rev2			NR-LU-10-Cons.			Standard Imaging		
		EXT	LIM	TOT	EXT	LIM	TOT	EXT	LIM	TOT
	EXT	41	14	55	45	10	55	51	4	55
	LIM	3	31	34	3	31	34	1	33	34
	TOT	44	45	89	48	41	89	52	37	89
Correctly Staged		72/89= 81%			85%			94%		
Overstaged		3/89= 3%			3%			1%		
Understaged		14/89= 16%			11%			5%		
PPV -- Extensive		41/44= 93%			94%			98%		
NPV -- Extensive		31/45= 69%			76%			89%		
Sensitivity		41/55= 75%			82%			93%		
Specificity		31/34= 91%			91%			97%		

where,

Overstaged = Patient with true limited disease said to have extensive disease. Such patients might not be offered potentially curative chest radiation in conjunction with combination chemotherapy.

Understaged = Patient with true extensive disease said to have limited disease. Such patients might receive potentially toxic radiation therapy that would be of no benefit.

PPV = Positive Predicted Value with respect to extensive disease; percent of cases predicted to be extensive disease that are truly extensive disease.

NPV = Negative Predicted Value with respect to extensive disease; percent of cases predicted to be limited disease that are truly limited disease.

TABLE 2 **Estimates of Imaging Performance Parameters for the Eligible Study Patients with Limited or Extensive Disease as Defined by NR-LU-10 Imaging or the Standard Battery of Tests Assuming that the NR-LU-10 Imaging is Correct, i.e., the discrepancies are resolved in favor of NR-LU-10 Imaging**

TRUE STAGE		NR-LU-10--Rev2			NR-LU-10-Cons.			Standard Imaging		
		EXT	LIM	TOT	EXT	LIM	TOT	EXT	LIM	TOT
	EXT	44	12	56	48	8	56	49	7	56
	LIM	0	33	33	0	33	33	3	30	33
	TOT	44	45	89	48	41	89	52	37	89
Correctly Staged		77/89= 87%			91%			89%		
Overstaged		0/89= 0%			0%			3%		
Understaged		12/89= 13%			9%			8%		
PPV -- Extensive		44/44=100%			100%			94%		
NPV -- Extensive		33/45= 73%			80%			81%		
Sensitivity		44/56= 79%			86%			88%		
Specificity		33/33=100%			100%			91%		

where,

Overstaged = Patient with true limited disease said to have extensive disease. Such patients might not be offered potentially curative chest radiation in conjunction with combination chemotherapy.

Understaged = Patient with true extensive disease said to have limited disease. Such patients might receive potentially toxic radiation therapy that would be of no benefit.

PPV = Positive Predicted Value with respect to extensive disease; percent of cases predicted to be extensive disease that are truly extensive disease.

NPV = Negative Predicted Value with respect to extensive disease; percent of cases predicted to be limited disease that are truly limited disease.

Per-Organ and Per-Lesion Analysis:

The Table 3 provides reconstructed results for all 333 identified organs in 89 evaluable patients considering standard battery of tests and further confirmation as "gold Standard." This table includes solid organs and bone marrow, and pleural effusions. This table states that the detection rate (sensitivity) for the identified organs is 74% with 95% confidence interval ranging from 69 to 79% (consensus interpretation). The Positive Predictive Value for NR-LU-10 Imaging relative to organs is 83% with 95% confidence interval ranging from 78 to 88%.

This Table 3 also includes the reconstructed results for all 610 known lesions in 89 evaluable patients considering standard battery of tests and further confirmation as "gold Standard." This table includes solid lesions and bone marrow, and pleural effusions. This table states that the detection rate (sensitivity) for the identified lesions is 63% with 95% confidence interval ranging from 58 to 67% (consensus interpretation). The Positive Predictive Value for NR-LU-10 Imaging relative to known lesions is 76% with 95% confidence interval ranging from 71 to 80%.

TABLE 3 Accounting of All Identified Organs and All Identified Lesions in 89 Evaluable Patients

TRUE STAGE	PER-ORGAN ANALYSIS						PER-LESION ANALYSIS				
		REV-2		CONSENSUS		TOT	REV-2		CONSENSUS		TOT
		+	-	+	-		+	-	+	-	
	+	191	87	207	71	278	275	211	304	182	486
	-	37	18	41	14	55	91	33	98	26	124
	TOT	228	105	248	85	333	366	244	402	208	610
Sensitivity		191/278= 69%		74%			57%		63%		
Specificity		18/55 = 33%		25%			27%		21%		
Accuracy		209/333= 63%		66%			50%		54%		
PPV-NR-LU-10		191/228= 84%		83%			75%		76%		
NPV-NR-LU-10		18/105= 17%		16%			14%		13%		

True Stage or "Gold Standard" is the Standard Battery of Tests plus Further Confirmation; + is Detected, - is Not Detected

TABLE 4A Summary Table -- Estimates of Imaging Performance Parameters (resolving the discrepancies in favor of Standard Tests)

Efficacy Parameters	Per-Lesion Analysis		Per- Organ Analysis		NR-LU-10 -- Per-Patient		Standard Tests -- Per-Patient
	Rev 2	Consensus	Rev 2	Consensus	Rev 2	Consensus	
Sensitivity	57%	63%	69%	74%	75%	82%	93%
95% CI	(52 , 61)	(58 , 67)	(63 , 74)	(69 , 79)	(61 , 85)	(69 , 91)	(82 , 98)
Specificity	27	21	33	25	91	91	97
95% CI	(19 , 35)	(14 , 29)	(21 , 47)	(15 , 39)	(76 , 98)	(76 , 98)	(85 , 100)
Accuracy	50	54	63	66	81	85	94
95% CI	(46 , 55)	(50 , 58)	(57 , 68)	(61 , 71)	(71 , 88)	(76 , 92)	(87 , 98)
PPV	75	76	84	83	93	94	98
95% CI	(70 , 79)	(71 , 80)	(78 , 88)	(78 , 88)	(81 , 99)	(83 , 99)	(90 , 100)
NPV	14	13	17	16	69	76	89
95% CI	(9 , 18)	(8 , 18)	(10 , 26)	(9 , 26)	(53 , 82)	(60 , 88)	(75 , 97)

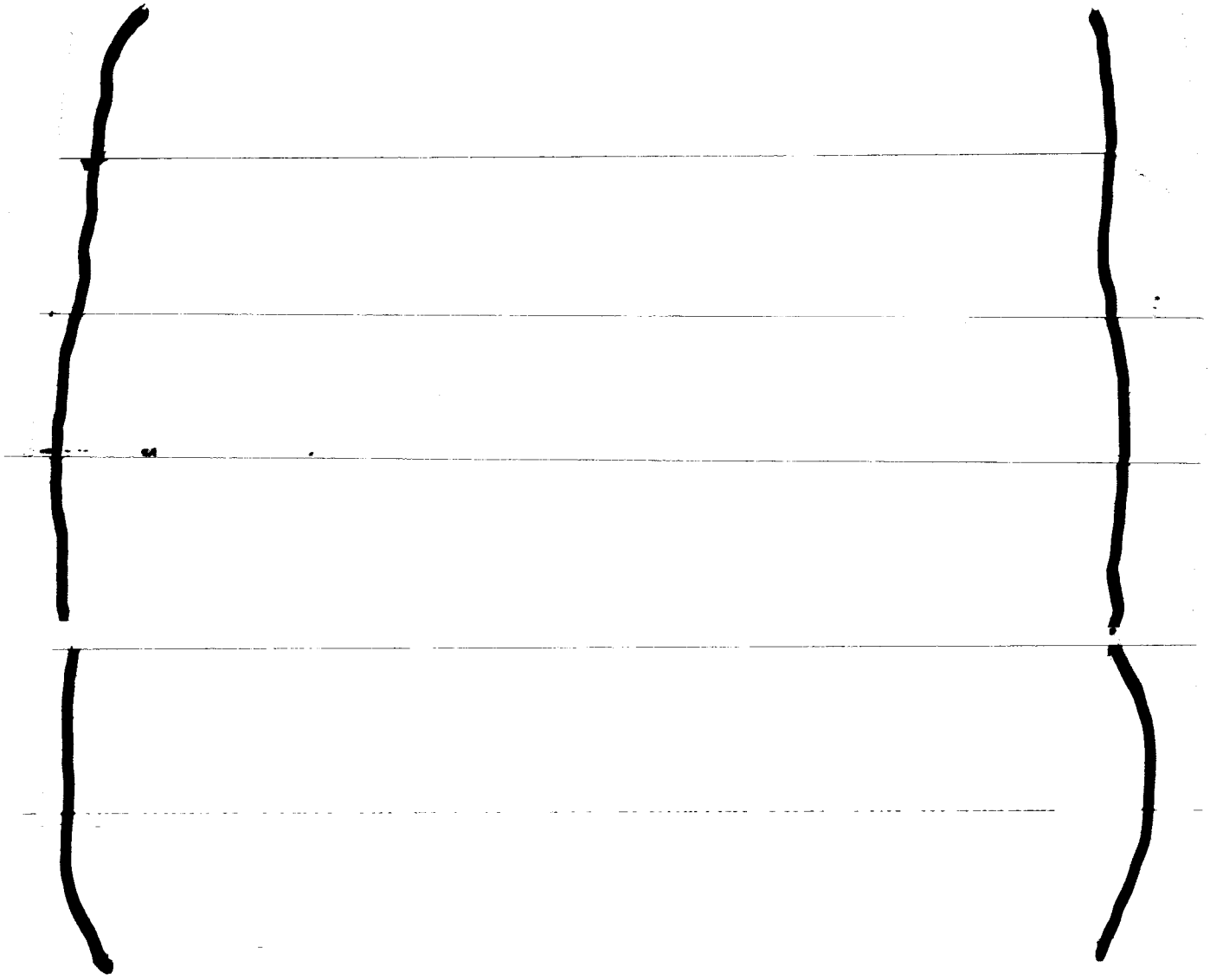
TABLE 4B Summary Table -- Estimates of Imaging Performance Parameters (resolving the discrepancies in favor of NR-LU-10 Scan)

Efficacy Parameters	Per- Lesion Analysis		Per- Organ Analysis		NR-LU-10 -- Per-Patient		Standard Tests -- Per-Patient
	Rev 2	Consensus	Rev 2	Consensus	Rev 2	Consensus	
Sensitivity	57%	63%	69%	74%	79%	86%	88%
95% CI	(52 , 61)	(58 , 67)	(63 , 74)	(69 , 79)	(66 , 88)	(74 , 94)	(76 , 95)
Specificity	27	21	33	25	100	100	91
95% CI	(19 , 35)	(14 , 29)	(21 , 47)	(15 , 39)	(91 , 100)	(91 , 100)	(76 , 98)
Accuracy	50	54	63	66	87	91	89
95% CI	(46 , 55)	(50 , 58)	(57 , 68)	(61 , 71)	(78 , 93)	(83 , 96)	(80 , 94)
PPV	75	76	84	83	100	100	94
95% CI	(70 , 79)	(71 , 80)	(78 , 88)	(78 , 88)	(93 , 100)	(94 , 100)	(84 , 99)
NPV	14	13	17	16	73	80	81
95% CI	(9 , 18)	(8 , 18)	(10 , 26)	(9 , 26)	(58 , 85)	(65 , 91)	(65 , 92)

Conclusions:

Tables 4A and 4B provide the summary results for various efficacy parameters. These Tables (4A & 4B) reveal that various estimates of the efficacy parameters (sensitivity, PPV, etc.) are consistently lower for the Rev2 than for the consensus interpretation; but this difference is not statistically significant. The sponsor has done an adequate job of explaining that there are no statistical differences in the staging parameters and in lesion and organ detection rates among the second blinded reviewer (Rev2) and consensus interpretations.

The Stages were determined by the standard battery of diagnostic imaging tests involving physical examination, chest X-ray and/or CT of the chest, CT of the head, CT of the abdomen, and nuclear medicine bone scan and further confirmation.



standard tests and Rev2 should be included in the labeling and indication.

The sponsor stated that "once any single test indicates extensive disease, no further testing improves the accuracy of staging." The sponsor also stated that five cases were correctly staged extensive by physical examination alone, all were detected by NR-LU-10 Imaging and none by other diagnostic imaging tests.

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The difference between the results of Rev2 and R2 is not clear from the information provided.

The sponsor has correctly pointed out that the detection rate and sensitivity of SCLC lesions or extensive disease by antibody NR-LU-10 imaging are significantly better than any single standard diagnostic modality alone.

Overall, the product appears to be useful in detecting extensive disease in a single test. The detection rate (sensitivity) of SCLC lesions/organs and extensive disease by antibody NR-LU-10 imaging also appear to be better than any single standard diagnostic modality alone.

Satish C. Misra 8/3/95

Satish C. Misra, Ph.D.
Mathematical Statistician

Concur: Peter A. Lachenbruch

Peter A. Lachenbruch, Ph.D., HFM-215
Chief, Biostatistics Branch/DBE

Statistical Review and Evaluation

Date: NOV 14 1995

PLA #: 94-0308

Applicant: Thomae/Boehringer Ingelheim (BI) GmbH

Name of Product: [redacted] -- the NR-LU-10 Fab Imaging Agent for Small Cell Lung Cancer

Document Reviewed: Responses to FDA Letter dated September 22, 1995 Submitted on October 31, 1995

Background:

Small Cell Lung Cancer (SCLC) accounts for 20% of all lung cancers, with approximately 30,000 new cases annually in the United States. Only 25% of patients with extensive disease (distance detectable metastases) achieve complete remission; the median survival is 33 weeks and only 1-3 percent of patients survive more than 3 years. In contrast, 60% of patients with limited disease (tumor confined to one hemithorax, mediastinum, ipsilateral supraclavicular nodes) achieve complete remission; median survival exceeds one year and as many as 25% may enjoy long-term survival. Distinguishing extensive from limited disease small cell lung cancer is critical for establishing prognosis and choosing therapy.

Accurate staging of SCLC is critical to determine prognosis and to facilitate appropriate therapeutic decisions, such as surgery, radiation, chemotherapy, or combination therapy. The standard procedures currently used to stage patients with SCLC include X-ray or radiographic computerized tomography (CT) of the chest, CT of the abdomen, CT of the head, nuclear medicine bone scanning, and invasive procedures, such as bone marrow aspiration or biopsy. This "standard battery of tests" subjects the patients to a series of injection (IV contrast and bone scan MDP) and imaging procedure over several days. The bone marrow aspiration and biopsy are invasive and moderately painful.

Monoclonal anti-body based diagnostic imaging offers the potential for detecting primary and metastatic cancer in multiple organs and anatomic sites with a single test and for revealing disease in tissues or areas not routinely assessed by other techniques. Suspicious areas requiring confirmation can be corroborated by a different procedure directed to the specific

site detected by antibody imaging.

[redacted] is a kit for the preparation of Technetium Tc 99m Labeled Muromonoab NR-LU-10 Fab for imaging small cell lung cancer (SCLC), and is indicated for the primary staging of patients with newly-diagnosed small cell lung cancer. It is a diagnostic imaging procedure to determine with a single test the stage of patients with SCLC. Nearly complete information is obtained in less than 24 hours following a single injection of the NR-LU-10 imaging. The radiolabeled antibody is expected to localize in sites of small cell lung cancer; gamma camera imaging then allows evaluation of multiple anatomic regions and organ systems with a single test. The results are useful to physicians and patients for making decisions among therapeutic options.

This was a phase III, multi-center trial of nonpregnant adult patients with a new, histologically-confirmed diagnosis of small cell lung cancer and at least one evaluable lesion. Patients had not received chemotherapy, radiation therapy, or any other investigational agent for this tumor before study entry. For entry onto the study, patients underwent a standard battery of diagnostic tests that included physical examination, X-ray or radiographic computed tomography (CT) of the chest, CT of the head, CT of the abdomen, nuclear medicine bone scan, and bone marrow aspiration.

Interpretation and review of the scintiscans was performed at three levels. The first evaluation, termed the unblinded review, was done at clinical site by an experienced nuclear medicine physician who had full knowledge of the patient's clinical status. A second evaluation, termed the blinded review, was performed by one of two nuclear medicine consultants (randomly selected) who had no knowledge of the patient's clinical status or the results of the first interpretation. The first and second evaluation were then compared. When there was a discrepancy, a third nuclear medicine consultant reviewed the images to provide a third opinion about those specific areas where the readings of the first and second reviewer differed. The third reviewer was blinded with regard to the patient's clinical history and had no knowledge of the results of the first two reviews except that there was a discrepancy within a specific anatomic area. Those lesions read as positive by two of the three reviewers are termed a consensus result.

There were 24 investigational sites with 96 enrolled patients, and 89 evaluable patients (met inclusion criteria). The average age of the patients was 61 years (range 34-88 years) with 77% males. About 56% of patients had extensive disease (distance detectable metastases), and remaining 42% of patients had limited

disease (tumor confined to one hemithorax, mediastinum, ipsilateral supraclavicular nodes).

The objectives of the study included (i) evaluation of safety, (ii) estimation of sensitivity and positive predicted value of NR-LU-10 imaging, and (iii) the comparison with standard diagnostic tests. The sponsor stated that standard stage obtained by using standard battery of tests including biopsy, bone marrow aspiration, further confirmation including NR-LU-10 imaging stage determined the true stage of SCLC.

Analysis and Comments:

Primary Analysis:

The focus of primary analysis is the results of evaluation by the second reviewer (R2), the blinded reviewer, who read all the scans without any of the diagnostic, clinical or technical information available to the first (on-site) reviewer. The stages (extensive or limited disease) were determined by the standard battery of diagnostic imaging tests involving physical examination, chest X-ray and/or CT of the chest, CT of the head, CT of the abdomen, and nuclear medicine bone scan and <u>further confirmation</u>. This was considered to be the "gold standard" for estimation purposes.

The staging results of 89 evaluable patients revealed 53 patients to be true extensive and 31 to be true limited. In five cases, there was a discrepancy that could not be resolved between the results of NR-LU-10 and the standard battery of tests (2 staged as limited by NR-LU-10 but extensive by standard, and 3 staged as extensive by NR-LU-10, but limited by standard). Further discussion between the sponsor and CBER led to the following decision based on mutual agreement, and fax transmission sent to CBER by the sponsor on November 9, 1995:

Patient Number	NR-LU-10 Stage	Standard Stage	Truth
[redacted]	Limited	Extensive	Extensive
	Extensive	Limited	Extensive
	Limited	Extensive	Limited
	Extensive	Limited	Extensive
	Extensive	Limited	Extensive

The database earlier submitted by the sponsor on Oct. 20, 1995 was corrected to include this information.

Throughout this report, the following definitions are used:

Sensitivity = True Positive Rate; Percent of patients with true extensive disease said to have extensive disease by diagnostic test.

Specificity = True Negative Rate; Percent of patients with true limited disease said to have limited disease by diagnostic test.

Accuracy = Correctly Staged Rate; Percent of patients with true extensive or limited disease said to have extensive or limited disease by diagnostic test.

Understaged = False Positive Rate; Percent of patients with true extensive disease said to have limited disease by diagnostic test. Such patients might receive potentially toxic radiation therapy that would be of no benefit.

Overstaged = False Negative Rate; Percent of patients with true limited disease said to have extensive disease by diagnostic test. Such patients might not be offered potentially curative chest radiation in conjunction with combination chemotherapy.

PPV -- Ext = Positive Predicted Value with respect to extensive disease; percent of cases predicted to be extensive disease by diagnostic test that are truly extensive disease.

NPV -- Ext = Negative Predicted Value with respect to extensive disease; percent of cases predicted to be limited disease by diagnostic test that are truly limited disease.

Note: The 95% confidence interval for accuracy, PPV and NPV for combined standard tests or for NR-LU-10 for extensive disease are conditional and do not take into account the variation in the population prevalence rate. These statistics are of limited value due to this dependence.

Per-Person Analysis:

Comparison with Combined Standard Tests:

TABLE 1 provides patient-based estimates of imaging performance parameters for the eligible study patients with limited or extensive disease as defined by NR-LU-10 imaging or the combined standard battery of tests based on the interpretations by the blinded second reviewer (R2). This Table reveals that there are no significant differences between the staging results of NR-LU-10 imaging and standard battery of tests ($p \geq 0.22$ for any difference).

The sensitivity of NR-LU-10 Imaging for extensive disease is 77% (95% Confidence Interval ranging from 64 to 87%, n = 57) with a PPV of 94% (95% confidence interval ranging from 82% to 99%, n = 47). The detection rate (sensitivity) of Standard Battery of Tests for extensive disease is 88% (95% Confidence Interval ranging from 76% to 95%, n = 57) with a PPV of 96% (95% confidence interval ranging from 87% to 100%, n= 52).

Therefore, a 95% confidence interval on PPV using NR-LU-10 MAb F(ab) for the diagnosis of extensive disease ranges from 82% to 99% (n=47); as compared to 95% confidence interval of 87% to 100% on PPV using combined standard battery of tests. The PPVs of the two diagnostic modalities are similar.

Comparison with Single Standard Test:

TABLE 2 provides a comparison with single standard test with NR-LU-10 imaging for patient-based estimates based on the interpretations by the blinded second reviewer (R2).

This table shows that the sensitivity and accuracy (TP + FN) of any single standard test (physical examination, chest X-ray, Physical exam & Chest X-ray together, CT - chest, CT - abdomen, Bone Scan) is consistently lower than the sensitivity and accuracy of NR-LU-10 alone in detecting extensive disease. The sample size is small to make valid comparisons as reflected in

wide confidence intervals exhibited in Table 2. This table also shows that PPV of any single test is similar to PPV of NR-LU-10 in detecting extensive disease. This implies that once a single test including physical exam and/or chest x-ray indicates extensive disease, NR-LU-10 can not provide any additional clinical utility for these patients.

The sponsor seems to confirm this. The sponsor stated that "once any single test indicates extensive disease, no further testing improves the accuracy of staging." [redacted]. The sponsor, however, provided reasons for using NR-LU-10 Imaging for these patients as it might be "quicker, safer, less painful, and provide more information than a local biopsy." [redacted] The sponsor also states that among the patients with no evidence for extensive disease by NR-LU-10 imaging, accuracy of diagnosing limited disease can be improved by the use of other tests such as CT examination of the abdomen, CT of the head, nuclear medicine bone scan, bone marrow aspiration and/or biopsy, and CT or X-ray of the chest."

TABLE 1 **Patient-Based Estimates of Imaging Performance Parameters for the Eligible Study Patients with Limited or Extensive Disease as Defined by NR-LU-10 Imaging or the Standard Battery of Tests Based on the Interpretations by the Blinded Second Reviewer (R2).**

	Standard Tests Combined				NR-LU-10 Imaging		
		Ext.	Lim.	Total	Ext.	Lim.	Total
True Stage	Ext.	50	7	57	44	13	57
	Lim.	2	30	32	3	29	32
Param-eters	Total	52	37	89	47	42	89
Sensitivity (True+)		50/57 = 88%			44/57 = 77%		
95% Confidence Interval		76% - 95%			64 - 87		
Specificity (True-)		30/32 = 94%			29/32 = 91%		
95% Confidence Interval		79 - 99			75 - 98		
Accuracy (Correctly Staged)		80/89 = 90%			73/89 = 82%		
95% Confidence Interval		82 - 95			72 - 89		
Understaged (False +)		7/57 = 12%			13/57 = 23%		
95% Confidence Interval		5 - 24			13 - 36		
Overstaged (False -)		2/32 = 6%			3/32 = 9%		
95% Confidence Interval		1 - 21			2 - 25		
PPV -- Extensive		50/52 = 96%			44/47 = 94%		
95% Confidence Interval		87 - 100			82 - 99		
NPV -- Extensive		30/37 = 81%			29/42 = 69%		
95% Confidence Interval		65 - 92			53 -82		

The 95% Confidence Intervals are based on exact Binomial test.

TABLE 2 **Comparison with Single Standard Test with NR-LU-10 Imaging for Patient-Based Estimates Based on the Interpretations by the Blinded Second Reviewer (R2).**

True Stage	Phys.Exam		Chest Xray		Phys/ChXray		CT-Chest		CT-Head		CT-Abdomen		Bone Scan		BMA/Biopsy		Total
	Ext	Lim	Ext	Lim	Ext	Lim	Ext	Lim	Ext	Lim	Ext	Lim	Ext	Lim	Ext	Lim	
Ext	8	49	2	55	10	47	5	52	12	45	33	24	24	33	16	41	57
Lim	1	31	0	32	1	31	0	32	0	32	2	30	0	32	0	32	32
Total	9	80	2	87	11	78	5	84	12	77	35	54	24	65	16	73	89
Sens	14		4		18		9		21		58		42		28		77*
95%CI	6 - 26		.4 - 12		9 - 30		3 - 19		11 - 34		44 - 71		29 - 56		17 - 42		64-87
Spec	97		100		97		100		100		94		100		100		91
95%CI	84 - 100		91 - 100		84 - 100		91 - 100		91 - 100		79 - 99		91 - 100		91 - 100		75-98
Acc	44		38		46		42		49		71		63		54		82
95%CI	33 - 55		28 - 49		35 - 57		31 - 53		30 - 60		60 - 80		52 - 73		43 - 65		72-89
PPV	89		100		91		100		100		94		100		100		94
95%CI	52 - 100		22 - 100		59 - 100		55 - 100		78 - 100		81 - 99		88 - 100		83 - 100		82-99
NPV	39		37		40		39		42		56		49		44		69
95%CI	28 - 50		27 - 48		29 - 51		28 - 49		30 - 54		41 - 69		37 - 62		32 - 60		53-82

* Estimates of the parameters for NR-LU-10

The 95% Confidence Intervals are based on Exact Binomial test. All the numbers for the parameter estimates are percentages.

Per-Organ Analysis:

One of the secondary objective of the study was to evaluate the detection of organs with known metastasis and the detection of known lesions in patients with small cell lung cancer.

There were a total of 333 identified organs in 89 evaluable patients. The sponsor excluded 26 solid organs with an uncertain diagnosis in the calculation of detection rates (sensitivity) [redacted] but they were used in calculating the clinical stage defined by NR-LU-10 Imaging. There were 14 "non-detected" organs by both tests subsequently found to be (i) first detected by NR-LU-10; or (ii) subsequently diagnosed as containing metastatic small cell lung cancer; or (iii) not further defined. There were 2 true negative organs discovered by NR-LU-10 Imaging not to contain small cell lung cancer. This reduced sponsor's number of known diseased organs to 274 out of 292 solid and bone marrow organs. The sponsor stated that the detection rate of diseased organs by NR-LU-10 Imaging procedure alone is 77% (212/274) with 95% confidence interval ranging from 71 to 81% [redacted]

The systematic exclusion of some organs makes the sponsor's numbers hard to interpret. The sponsor's method may work well on the clear cut cases, but not on the fuzzy ones. Therefore, the results for all 333 identified organs in 89 evaluable patients were reconstructed based on raw data provided assigned the stage of "?" SCLC to no SCLC as suggested by George Mills. These results are summarized in Table 3 below.

Table 3 provides accounting of all identified organs in 89 evaluable patients based on interpretation of blinded reviewer R2 and SCLS diagnosis. This table states that the detection rate (sensitivity) for the identified organs is 71% with 95% confidence interval ranging from 65 to 76%. The Positive Predictive Value for NR-LU-10 Imaging relative to organs is 84% with 95% confidence interval ranging from 78 to 88%.

Table 4 provides the detection rates of diseased organs by the NR-LU-10 imaging procedure alone based on second blinded reviewer - R2. The highest detection rate occurs in lung (87% with 95% confidence interval ranging from 78 to 94%); and the lowest detection rates are in the areas of sup cutaneous, subcutaneous, nodes-masses-abdomen, pelvis & groin, head and artifact (all 0%).

TABLE 3 Accounting of All Identified Organs in 89 Evaluable Patients Based on Interpretation of Blinded Reviewer R2 And SCLS Diagnosis

		NR=LU-10 Imaging Detected	Not Detected	Total
True SCLC Diagnosis	Yes	194	80	274
	No	38	21	59
	Total	232	101	333

	Estimate	95% Confidence Interval (%)
Sensitivity	=194/274 = 71%	69-80
Specificity	= 21/59 = 36%	14-37
Accuracy	=215/333 = 65%	61-71
PPV--NR-LU-10	=194/232 = 84%	79-88
NPV--NR-LU-10	= 21/101 = 21%	9-24

Notes: This table includes solid organs and bone marrow, and pleural effusions.

The confidence intervals provided here do not take into account the correlated nature of the responses of organs within individual. The confidence intervals are not based on appropriate standard errors. They are given here to reproduce and compare the confidence intervals provided by the sponsor.

Table 4: Detection Rates of Diseased Organs by the NR-LU-10 Imaging Procedure Alone Based on the Second Blinded Reviewer - R2

Organ/Site	Detection Rate (%)	95% Confidence Interval
1. Brain	3/12 = 25%	5 - 57 %
2. Lung	69/79 = 87%	78 - 94 %
3. Liver	17/27 = 63%	42 - 81 %
4. Spleen	0/2 = 0%	0 - 78 %
5. Bone	21/26 = 81%	61 - 93 %
6-7. Sup/Sub Cutaneous	0/1 = 0%	0 - 95 %
8. Nodes-Neck/Axilla	5/8 = 63%	24 - 91 %
8X-9. Lymph Nodes Supraclavicular/Mediastinum	56/66 = 85%	74 - 92 %
10-12. Nodes/Masses-Abdomen Pelvis, Groin	0/5 = 0%	0 - 45 %
13. Other -- Head	0/1 = 0%	0 - 95 %
14-17. Other -- Thorax, Abdomen, Breast	2/15 = 13%	2 - 40 %
18. Pleural Effusion	4/9 = 44%	14 - 79 %
19. Bone Marrow	13/17 = 76%	50 - 93 %
22. Pleural Mass	4/6 = 67%	22 - 96 %
TOTAL	194/274 = 71%	65 - 76 %

Notes: This table includes solid organs and bone marrow, and pleural effusions.

The confidence intervals provided here do not take into account the correlated nature of the responses of organs within individual. The confidence intervals are not based on appropriate standard errors. They are given here to reproduce and compare the confidence intervals provided by the sponsor.

Per-Lesion Analysis:

There were a total of 610 known lesions (all sizes) in 89 evaluable patients. The sponsor stated that the detection rate of known lesions by NR-LU-10 Imaging procedure alone is 65% (332/507) with 95% confidence interval ranging from 61 to 69% [redacted] Other lesions (610-507=103) were excluded from the analysis for reasons similar to those given in per-organ section of this report. The systematic exclusion of some lesions makes the sponsor's numbers hard to interpret. The results for all 610 known lesions in 89 evaluable patients were reconstructed and are summarized in Table 5 below.

This table states that the detection rate (sensitivity) for the identified organs is 59% with 95% confidence interval ranging from 54 to 63%. The Positive Predictive Value for NR-LU-10 Imaging relative to known lesions is 80% with 95% confidence interval ranging from 76 to 84%.

TABLE 5 Accounting of All Identified Lesions in 89 Evaluable Patients Based on Interpretation of Blinded Reviewer R2 And SCLS Lesion Diagnosis

		NR=LU-10 Imaging		
		Detected	Not Detected	Total
True SCLC Diagnosis	Yes	297	210	507
	No	73	30	103
	Total	370	240	610

	Estimate	95% Confidence Interval (%)
Sensitivity	=297/507 = 59%	54-63
Specificity	= 30/103 = 29%	21-39
Accuracy	=327/610 = 68%	65-71
PPV--NR-LU-10	=297/370 = 80%	76-84
NPV--NR-LU-10	= 30/240 = 13%	9-17

Note: This table includes solid lesions and bone marrow, and pleural effusions.

The confidence intervals provided here do not take into account the correlated nature of the responses of organs within individual. The confidence intervals are not based on appropriate standard errors. They are given here to reproduce and compare the confidence intervals provided by the sponsor.

Conclusions:

The detection rate (sensitivity) of NR-LU-10 Imaging for extensive disease is 77% (95% Confidence Interval ranging from 64 to 87%, n = 57) with a PPV of 94% (95% confidence interval ranging from 82% to 99%, n = 47). The detection rate (sensitivity) of Standard Battery of Tests for extensive disease is 88% (95% Confidence Interval ranging from 76% to 95%, n = 57) with a PPV of 96% (95% confidence interval ranging from 87% to 100%, n= 52). The PPVs of the two diagnostic modalities were similar.

The sensitivity and accuracy of any single standard test (physical examination, chest X-ray, Physical exam & Chest X-ray together, CT - chest, CT - abdomen, Bone Scan) is consistently (and significantly in most cases) lower than the sensitivity and accuracy of NR-LU-10 alone in detecting extensive disease. The sample size is small to make valid comparisons. The PPV of any single test is similar to PPV of NR-LU-10 in detecting extensive disease. This implies that once a single test including physical exam and/or chest x-ray indicates extensive disease, NR-LU-10 can not provide any additional clinical utility for these patients.

Further analysis related to accounting of all identified organs in 89 evaluable patients based on interpretation of blinded reviewer R2 and SCLS diagnosis revealed that the detection rate (sensitivity) for the identified organs is 71% with 95% confidence interval ranging from 65 to 76%. The Positive Predictive Value for NR-LU-10 Imaging relative to organs is 84% with 95% confidence interval ranging from 78 to 88%.

The highest detection rate occurs in lung (87% with 95% confidence interval ranging from 78 to 94%); and the lowest detection rates are in the areas of sup cutaneous, subcutaneous, nodes-masses-abdomen, pelvis & groin, head and artifact (all 0%).

Further analysis related to accounting of all identified lesions in 89 evaluable patients based on interpretation of blinded reviewer R2 and SCLS diagnosis revealed that the detection rate (sensitivity) for the identified lesions is 59% with 95% confidence interval ranging from 54 to 63%. The Positive Predictive Value for NR-LU-10 Imaging relative to known lesions is 80% with 95% confidence interval ranging from 76 to 84%.

Satish C. Misra 11/14/95

Satish C. Misra, Ph.D.
Mathematical Statistician

Concur: Peter A Lachenbruch

Peter A. Lachenbruch, Ph.D., HFM-215
Chief, Biostatistics Branch/DBE

Statistical Review and Evaluation

Date: NOV 15 1995

PLA #: 94-0308

Applicant: Thomae/Boehringer Ingelheim (BI) GmbH

Name of Product: [redacted] -- the NR-LU-10 Fab Imaging Agent for Small Cell Lung Cancer

Document Reviewed: Population Prevalence

Please add the following Table 1a to previously issued DBE memo dated Nov 14, 1995. This Table provides predicted estimates of the accuracy, PPV and NPV based on assumed population prevalence rates for the extensive disease to be 69% (sponsor's assumption), 75% and 60%. Note that the estimates do not change that much and actually are similar to the observed estimates.

Satish C. Misra

Satish C. Misra, Ph.D. 11/14/95
Mathematical Statistician

Concur: Peter A. Lachenbruch

Peter A. Lachenbruch, Ph.D., HFM-215
Chief, Biostatistics Branch/DBE

TABLE 1a Patient-Based Estimates of Imaging Performance Parameters for the Eligible Study Patients Adjusting for Disease Prevalence in the Population Based on the Interpretations by the Blinded Second Reviewer (R2).

Parameters	Study Data		Predicted assuming the prevalence rate for extensive disease is					
			69%		75%		60%	
	Standard	NR-LU-10	Standard	NR-LU-10	Standard	NR-LU-10	Standard	NR-LU-10
Sensitivity	88 %	77 %	DO NOT CHANGE					
Specificity	94%	91 %						
Accuracy	90 %	82 %	90	81	89	80	90	82
PPV	96 %	94 %	97	95	98	96	95	93
NPV	81 %	69 %	77	64	72	57	84	73

The predicted rates are calculated as follows:

Predicted Accuracy = p x Sensitivity + (1-p) x Specificity

Predicted PPV = p x Sensitivity / ((p x Sensitivity + (1-p) x (1 - Specificity))

Predicted NPV = (1-p) x Specificity /((1-p)x Specificity + p x (1 - Sensitivity))

Where p = population prevalence rate for the extensive disease.

These values reproduce the sponsor's values for p = 69%.

Statistical Review and Evaluation

Date: JAN 4 1996

PLA #: 94-0308

Applicant: Thomae/Boehringer Ingelheim (BI) GmbH

Name of Product: [redacted] -the NR-LU-10 Fab Imaging Agent for Small Cell Lung Cancer

Document Reviewed: Sensitivity Analysis

The Advisory Committee suggested additional sensitivity analyses done on this PLA that include routine clinical practice, i.e., what happens if the patient with extensive disease identified with routine physical exam alone, chest X-ray, CT scan of Chest, CT scan of Head and CT scan of Abdomen are deleted step-by-step from the analyses. These analyses are presented in Table 1.

This Table reveals that the sensitivity of the NR-LU-10 scan drops to 62% and 95% confidence interval ranging from 32 to 86% (n=43) from overall sensitivity of 77% and 95% confidence interval ranging from 64 to 87% (n=89) if all patients diagnosed with extensive disease by physical exam, chest x-ray, CT scan of chest, head & abdomen are dropped from the analysis. Due to small sample size for this group, the 95% exact confidence intervals based on binomial distribution are also much wider as compared to the overall data. Likewise, the sample positive predictive value for this group is 73% with 95% confidence interval ranging from 39 to 94% as compared to the overall PPV of 94% with 95% confidence interval ranging from 82 to 99%.

Satish C. Misra, Ph.D.
Mathematical Statistician

Concur:

Peter A. Lachenbruch, Ph.D., HFM-215
Chief, Biostatistics Branch/DBE

TABLE 1: SENSITIVITY ANALYSIS AFTER DELETING PATIENTS WITH EXTENSIVE DISEASE DETECTED BY VARIOUS STAGES OF THE EXAMINATION PROCESS

True Stage	Delete Extensive by Physical Exam Alone		Delete Extensive by Physical Exam and Chest X-ray		Delete Extensive by Physical, Chest Xray & CT-Chest		Delete Extensive by Physical, Chest Xray , CT-Chest & CT-Head		Delete Extensive by Physical, Chest Xray, CT-Chest, Head & Abdomen		All Data-- No Deletion	
	Ext.	Lim.	Ext.	Lim.	Ext.	Lim.	Ext.	Lim.	Ext.	Lim.	Ext.	Lim.
Ext.	36	13	34	13	31	13	27	8	8	5	44	13
Lim.	3	28	3	28	3	28	3	28	3	27	3	29
Total	39	41	37	41	34	41	30	36	11	32	47	42
Sensitivity	73 %		72 %		70 %		77 %		62 %		77 %	
95% CI	(58 - 85)		(57 - 84)		(52 - 83)		(60 - 90)		(32 - 86)		(64 - 87)	
Specificity	90		90		90		90		90		91	
95% CI	(74 - 98)		(74 - 98)		(74 - 98)		(74 - 98)		(73 - 98)		(75 - 98)	
Accuracy	80		79		79		83		81		82	
95% CI	(70 - 88)		(69 - 88)		(68 - 87)		(72 - 91)		(67 - 92)		(72 - 89)	
PPV	92		92		91		90		73		94	
95% CI	(79 - 98)		(78 - 98)		(76 - 98)		(73 - 98)		(39 - 94)		(82 - 99)	
NPV	68		68		68		78		84		69	
95% CI	(52 - 82)		(52 - 92)		(52 - 82)		(60 - 90)		(67 - 95)		(53 - 82)	